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Studies on the Flavor Aversions Induced by Trialkyltin Compounds

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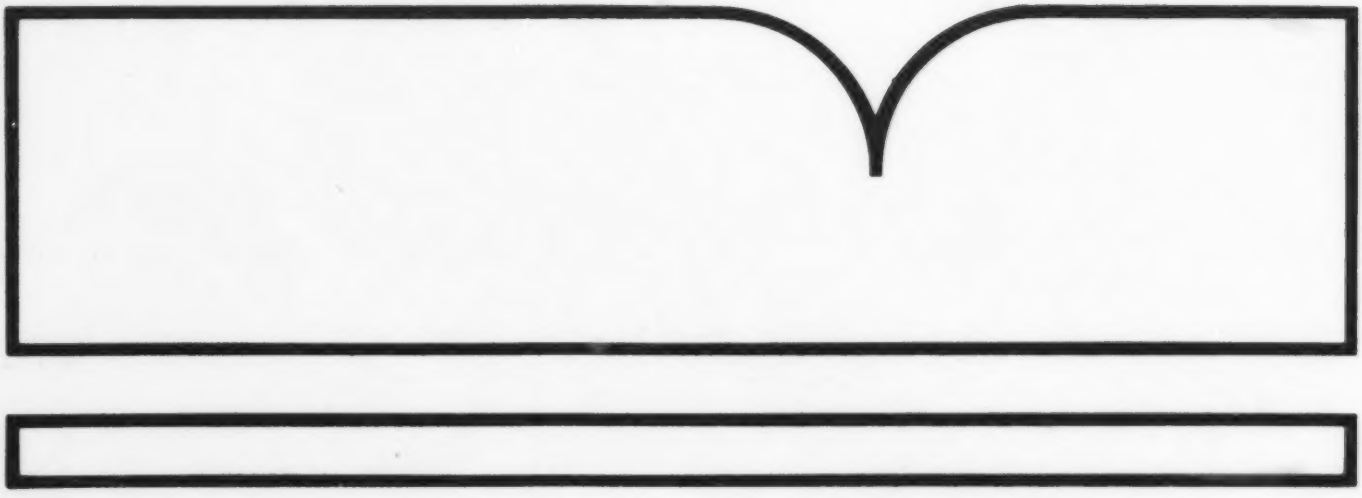

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16. ABSTRACT

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Studies on the Flavor Aversions Induced by Trialkyltin Compounds[1,2,3]

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MacPHAIL, R. C. *Studies on the flavor aversions induced by trialkyltin compounds.* NEUROBEHAV. TOXICOL. TERATOL. 4(2) 225–230, 1982.—These experiments were undertaken to determine the suitability of a flavor-aversion-conditioning paradigm for detecting the effects of trimethyltin and triethyltin. Both organotins produced flavor aversions whose magnitude depended jointly on the dosage administered and the number of flavor-organotin pairings. Estimated ED 50s (for triethyltin, 1.8 mg/kg; for trimethyltin, 3.1 mg/kg) were smaller than the dosages reported to affect other classes of behavior, but nevertheless represented a substantial percentage (25–45%) of the respective published LD-50 values. Flavor-aversion conditioning may represent a valuable tool for studying the effects of organic and inorganic heavy metals.

Trimethyltin Triethyltin Flavor aversion

ORGANOTINS form a broad category of compounds that are widely used commercially and which produce a multitude of biological effects [42]. Mono- and di-substituted organotin compounds are primarily used industrially in the manufacture of polyvinyl chloride and polyurethane foams. Tetrasubstituted organotins are used mainly in the preparation of other organotin compounds. Many trisubstituted organotins have been widely used as agricultural, marine and general biocides, most notably tributyl-, triphenyl- and tricyclohexyl-tin. Although trimethyl- and triethyl-tin have been used in fewer agricultural and industrial contexts, they are being increasingly used in research because of their prominent effects on behavior and the nervous system. Triethyltin produces cerebral edema in adult rats that is associated with intramyelinic vascuolation [26]. Repeated treatment of adult rats produces ataxia and hindlimb paralysis, which are generally reversible if dosing is stopped before the animals become severely debilitated [26]. Acute and short-term-repeated treatment of neonate rats produces persistent hyperactivity in adults and a different profile of central nervous system effects that are thought to be due to the inhibitory effect of triethyltin on cellular respiration. Trimethyltin produces destruction of portions of the hippocampus and surrounding area by an unknown mechanism [1,8]. Acute treatment of adult rats produces hyperactivity under many test conditions [35]; acute treatment of adult rats with large dosages induces a multifaceted syndrome of behavioral change somewhat similar to that produced by lesions of the limbic system [14].

There is now great concern over the development of test methods for detecting and characterizing the behavioral and neurological consequences of exposure to toxic substances [12, 19, 29]. One very promising method involves flavor-aversion conditioning. Garcia and his colleagues, for example, showed that rats' preferences for distinctly flavored solutions could be simply yet substantially reduced by pairing flavor intake with exposure to x-irradiation ([15]; for early review see [32]). Numerous subsequent experiments have both replicated these findings and extended them to include a wide array of drugs and other biomedically relevant chemicals. The ease and rapidity with which flavor-aversion tests can be carried out make them choice candidates for the routine preliminary assessment of neurotoxicants. The present series of experiments was therefore undertaken to determine the suitability of a flavor-aversion-conditioning paradigm for detecting the effects of trimethyltin and triethyltin. These experiments were part of a research program on flavor-aversion paradigms and their use in assessing the effects of agricultural, industrial and environmentally relevant chemicals. Flavor aversions have already been produced by arsenic [36], cadmium [24], copper sulfate [10,27], lead [11,20], methylmercury [6,22], pesticides such as chlordimeform [25] and 2, 4, 5-T [37,38], and acrylamide [3]. In addition, Leander and Gau [20] have recently shown

[1]A preliminary report of a portion of these data was presented at the annual conference of the Society of Toxicology, 1981 (*The Toxicologist* 1: 44–45, 1981).

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[3]This manuscript has been reviewed by the Health Effects Research Laboratory, U. S. Environmental Protection Agency, and approved for publication. Mention of trade names or commercial products does not constitute endorsement of recommendation for use.

that flavor aversions can be conditioned by triethyltin. The present series of experiments involved a systematic replication of the Leander and Gau [20] findings for triethyltin, and an extension to collect data on the flavor-aversions conditioned by trimethyltin.

METHOD

Animals

Adult male Long-Evans-derived (hooded) rats (Charles River Breeding Laboratories, Wilmington, MD) were used throughout except in one experiment (Experiment IV) which also used adult females. The rats were housed in groups of two or three in clear plastic cages (45×24×20 cm) with direct bedding and with food (Purina Laboratory Chow No. 5001, St. Louis, MO) provided ad lib. Cages were located in a temperature-controlled (21±0.6°C) colony room in which artificial lighting was provided from 0600 to 1800 hr daily.

Apparatus

The test apparatus was the same as described previously [25] and briefly consisted of a rack of small metal ceiling-suspended cages (Wahmann Mfg. Co., Timmonium MD, 24.5×18×18 cm) to which either one or two fluid-filled glass bottles with metal drinking spouts could be attached.

Procedure

In general, the procedures were similar to those described previously [25] although unique details are given below for each of the experiments. All rats were first acclimated to the colony room for several days and then placed on a 23-1/2 hr water-deprivation schedule. Tap water was provided for 30 min daily to individual rats in the test cages. The position of the water bottle was counterbalanced for each rat across test sessions and across rats for any one test session. Once intakes had stabilized, each rat was given access to one bottle containing tap water and one containing a 0.1% (w/v) solution of sodium saccharin, or to saccharin alone, for one 30-min session. Experiment II differed in that the distinctive flavor was 0.9% saline solution. Approximately 20 min after the end of the session, the rats received either a dosage of the toxicant, the toxicant vehicle, or no treatment. Six rats were generally included in each treatment group. All rats continued to receive limited acess to tap water alone for the next two sessions. On the third session after dosing, each rat received concurrent access to tap water and the flavored solution. In some experiments, the same treatment was administered again to each rat and followed by concurrent availability of tap water and flavored solution three sessions later; in different experiments, this cycle was in effect for a total of two to six pairings of flavor availability and toxicant administration (see below).

Experiment I: Triethyltin. This experiment provided normative data on the flavor aversions produced by triethyltin, and preliminary data on the effect of repeated pairing of flavor intake and triethyltin administration. After six days of adaptation to limited water availability, rats were given concurrent access to water and saccharin solution for 30 min and then approximately 20 min later, either triethyltin or the normal saline vehicle. Saccharin preference was determined three days later, as described above, and followed by a second administration of triethyltin or the saline vehicle, and a final determination of saccharin preference three days later. Triethyltin-Br (Alfa Products, Danvers, MA) was dissolved in the saline vehicle and administered IP in a volume of 1 ml/kg body weight, in dosages of 0.375, 0.75, 1.5 or 3.0 mg of the base/kg body weight. Each treatment group, including a vehicle-control group, was comprised of 6 rats. An additional 6 rats received access to saccharin and water in the test cages, and were treated with 1.5 mg/kg triethyltin, but were not otherwise adapted to the test cages and received access to water in their home cages. This group was included to determine the importance of direct experience with the test environment during stabilization of restricted water intakes.

Experiment II: Triethyltin. This experiment extended the above findings to include more pairings of flavor availability with triethyltin administration, and a different flavor stimulus. The design of this experiment was very similar to that of Experiment I except that the distinctively flavored solution was 0.9% saline, and flavor intake was determined after each of five or six pairings of the flavor with triethyltin. Groups of six rats received 0.188, 0.375, 0.75 or 1.5 mg of triethyltin base/kg body weight, or the normal saline vehicle, as described above for Experiment I. Previously all rats had been studied in a different test environment and had received a single pairing of saccharin availability and triethyltin administration, after which choice of saccharin was determined on five occasions. The test arrangement proved to be inappropriate for our purposes and therefore the rats were reassigned to groups and adapted to restricted water availability in the cages described above for an additional 11 days. Triethyltin in this experiment was administered more than five weeks after the initial treatments.

Experiment III: Trimethyltin. This experiment provided normative data on the flavor aversions induced by trimethyltin and on the efficacy of repeated pairings of flavor intake and trimethyltin administration. After 11 days of adaptation to limited water availability, all rats received 30 min access to saccharin solution and approximately 20 min later an injection of trimethyltin, normal saline, or no treatment. Trimethyltin-OH (K and K Laboratories, Plainview NY) was dissolved in normal saline solution and injected IP, in a volume of 1 ml/kg body weight, in dosages of 0.625, 1.25, 2.5 and 5.0 mg of base/kg body weight. Six rats comprised each treatment group. Relative saccharin intake was determined at three-day intervals after each of three pairings of saccharin availability and trimethyltin administration.

Experiment IV: Trimethyltin. This experiment determined whether there were sex differences in the flavor aversions induced by a large dosage of trimethyltin. After 7 days of adaptation to limited water availability, male and female rats received 30 min access to saccharin solution and, approximately 20 min later, an IP injection of trimethyltin-Cl (5 mg of base/kg body weight) or the normal saline vehicle (1 ml/kg body weight). Three days later saccharin preferences were determined. Six rats comprised each treatment group. Trimethyltin-Cl was obtained from the same source as in Experiment III.

Data Analysis

In all experiments, treatment groups were compared on the third day following toxicant administration for effects on total fluid intake (expressed in ml) and relative saccharin (or saline) intake (expressed as a proportion of total intake). In addition, in some experiments estimates of ED-50 values were made graphically: Average relative saccharin intake of

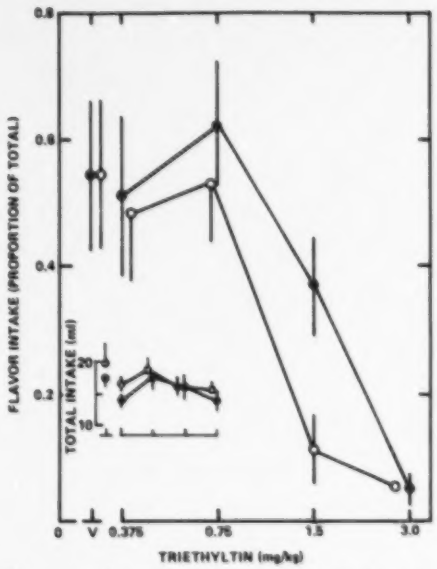

FIG. 1. Flavor aversions induced by triethyltin. Each symbol represents the average effect ± SEM of the saline vehicle (V) or a dosage of triethyltin on the saccharin intake of rats (N=6 per group), expressed as a proportion of the total intake. Effects of each treatment on total intake are shown in the insert. Solid symbols represent the effects of a single pairing of flavor and toxicant and open symbols represent the effects of two flavor-toxicant pairings.

the vehicle-control rats was first determined and divided by two. A horizontal line was drawn from that value on the y-axis to its point of intersection with the dose-effect function, from which a perpendicular was dropped to the x-axis. The resulting ED-50 value was estimated by interpolation.

RESULTS

Experiment I: Effects of Triethyltin

Saccharin intake (expressed as a proportion of total intake) did not differ between rats receiving the two smallest dosages of TET and those receiving the saline vehicle, but was decreased in an orderly fashion in rats receiving the two largest dosages (Fig. 1). The ED 50 was estimated to be 1.8 mg/kg. The flavor aversion produced by 1.5 mg/kg was augmented after a second pairing of saccharin and TET, whereas the effect of smaller and larger dosages remained unchanged. Figure 1 also shows there was no systematic effect of TET on total fluid intake.

Table 1 compares the effect of 1.5 mg/kg of TET on saccharin intake of rats that were adapted to limited fluid availability in the test cages and of those placed in the test cages on only the days when saccharin or saccharin and water were available. Data for the former group (A) were taken from Fig. 1. Although the average effect of TET is comparable for both groups after each saccharin-TET pairing, individual variability was substantially greater on both occasions for the group (B) not previously adapted to the test cages.

TABLE 1

COMPARISON OF THE EFFECTS OF TRIETHYLTIN (1.5 mg/kg) ON SACCHARIN INTAKE (AS PROPORTION OF TOTAL INTAKE)

GROUP	TEST 1	TEST 2
A	0.37 ± 0.08	0.11 ± 0.05
B	0.42 ± 0.14	0.22 ± 0.10
$\frac{\text{SEM - B}}{\text{SEM - A}}$	1.75	2.00

Group A had extensive exposure to the test chambers whereas Group B did not. Values are means ± SEM for groups of six rats.

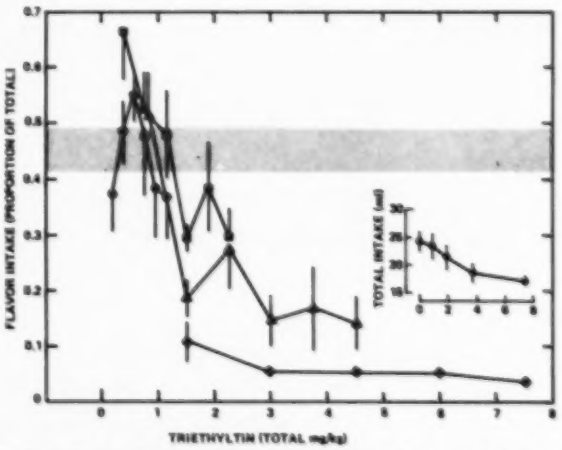

FIG. 2. Flavor aversions induced by triethyltin. Each symbol represents the average effect ± SEM of triethyltin (●, 0.188 mg/kg; ■, 0.375 mg/kg; ▲, 0.75 mg/kg; and ◆, 1.5 mg/kg) on the saline intake of rats (N=6 per group) expressed as a proportion of total intake. Flavor availability and triethyltin were paired on 5 or 6 occasions. The shaded region represents the range of average relative saline intakes of rats receiving five repeated pairings of flavor and the triethyltin vehicle. Values on the abscissa represent the total amount of triethyltin administered. Insert shows the effect of triethyltin (total dosages) on total intake after five pairings of flavor intake and triethyltin administration.

Experiment II: Effects of Triethyltin

On the first post-TET choice test, rats receiving 1.5 mg/kg displayed a prominent aversion to the saline-flavored solution whereas rats receiving smaller dosages were similar to vehicle-treated rats and indifferent in their intake of water and saline solutions (Fig. 2). However, Fig. 2 also shows that repeated pairing of flavor intake with TET enhanced the flavor aversion produced by 1.5 mg/kg; flavor aversions also became evident at smaller dosages (0.375 and 0.75 mg/kg) of TET. The functions relating relative flavor intake to the total

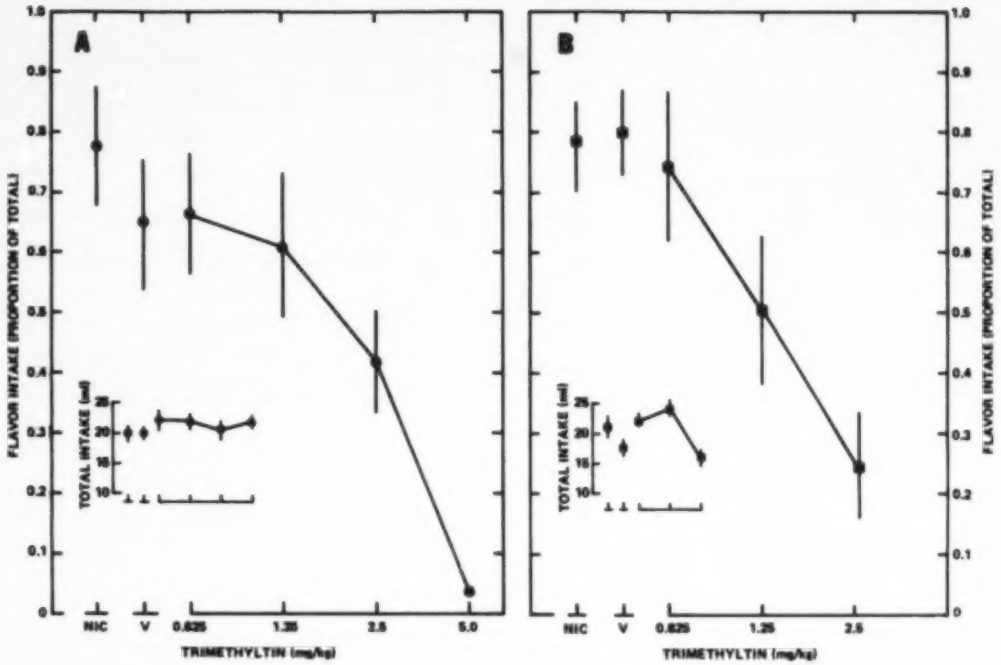

FIG. 3. Flavor aversions induced by trimethyltin. Each symbol represents the average effect ± SEM of no treatment (NIC), the saline vehicle (V) or dosages of trimethyltin on the saccharin intake of rats (n=6 per group), expressed as a proportion of total intake, after one (A) or three (B) flavor-toxicant pairings. Inserts show the effects of each treatment on total intake.

dosage administered showed considerable overlap in the effects of all but the largest dosage of TET. Total fluid intake was inversely related to TET dosage; the insert in Fig. 2 shows the effect of TET on total intake after the fifth pairing of flavor intake with toxicant administration.

Experiment III: Effects of Trimethyltin

The smallest dosage of TMT (0.625 mg/kg) had no effect on relative saccharin intake whereas the largest dosage (5.0 mg/kg) produced an almost maximal aversion to saccharin (Fig. 3). Intermediate dosages of TMT produced intermediate effects. The ED 50 was estimated to be 3.1 mg/kg. None of the dosages produced a change in total fluid intake. The flavor aversion produced by 2.5 mg/kg was more pronounced after three flavor-toxicant pairings. A second administration of 5.0 mg/kg proved to be lethal to all treated rats. Figure 3 also shows that the flavor aversions induced by TMT were non-systematically related to its effects on total intake.

Experiment IV: Effects of Trimethyltin

Figure 4 shows that regardless of sex, prominent flavor (saccharin) preferences were obtained in vehicle-treated rats whereas equally prominent flavor aversions were obtained in TMT-treated (5 mg/kg) rats. Sex differences were evident in total fluid intake, but for either sex the total intake did not differ between treatment groups (data not shown).

DISCUSSION

Administration of triethyltin or trimethyltin to rats shortly after consuming a distinctively flavored solution produced aversions to that flavor that depended on both the dosage and the number of flavor-toxicant pairings. Such conditioned flavor aversions have been demonstrated after exposure to x-irradiation (e.g., [15]) and a wide variety of psychotropic drugs (see [33]). It is only recently, however, that flavor aversions produced by agricultural, industrial and environmental chemicals have received experimental attention. Together with other results, the present finding of flavor aversions produced by trimethyltin and triethyltin, suggests that conditioned-flavor-aversion paradigms may represent a valuable tool for studying toxic heavy metals.

A single pairing of flavor availability and triethyltin (IP) produced flavor aversions that had an ED 50 of 1.8 mg/kg, and which were maximal at 3.0 mg/kg (Experiment I). After a second flavor-triethyltin pairing, effects were also produced by 1.5 mg/kg. In Experiment II, in which flavor and toxicant were paired several times, flavor aversions were noticeable in rats receiving 0.75 mg/kg. These results are in good agreement with those obtained by Leander and Gau [20] for rats receiving a different salt form of triethyltin, by a different route of administration, and tested under somewhat different conditions. By comparison, the locomotor activity of rats in a figure-eight maze was decreased by only about 30% after 3.0 mg/kg of SC triethyltin [31]. In addition Squibb *et al.* [39] reported behavioral effects of triethyltin (PO) only during the second week of twice-weekly dosing of rats with 2

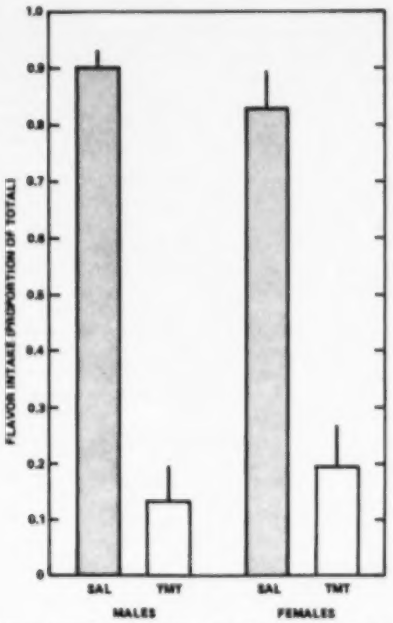

FIG. 4. Flavor aversions induced by trimethyltin. Each histogram represents the average effect + SEM of the saline vehicle (SAL) or 5.0 mg/kg of trimethyltin (TMT) on saccharin intake, expressed as a proportion of total intake, of male and female rats.

mg/kg. The present data together with those of Leander and Gau [20], indicate that substantial flavor aversions can be produced by triethyltin at dosages that have much less effect on other classes of behavior.

The LD50 for acute triethyltin has been determined to be between 4.0 and 5.7 mg/kg, and is somewhat independent of the route of administration [4,40]. Therefore, the ED 50 for triethyltin obtained after one flavor-toxicant pairing is between 32 and 45% of the reported LD50 values. Although flavor aversions were obtained at smaller dosages when they were repeatedly paired with flavor intake, the total amount of triethyltin actually delivered represents an even greater percentage of the reported LD50. Thus, triethyltin produces many prominent behavioral effects, and in the absence of grossly observable signs of intoxication, but the effective dosages are nevertheless a substantial fraction of those producing lethality. Some caution is appropriate, however, in interpreting these data since the LD50 values may be unusually low. In Experiment II, for example, no deaths were obtained in rats treated repeatedly with 1.5 mg/kg. Similarly, Squibb *et al.* [39] noted lethal effects in rats after the third administration of twice-weekly 3.0 mg/kg but not after the second administration.

A single pairing of flavor availability and trimethyltin (IP) produced flavor aversions that had an ED 50 of 3.1 mg/kg and that were maximal at 5.0 mg/kg. Flavor aversions were also produced by 2.5 mg/kg after repeated pairing of flavor and toxicant. At the same time, however, a second injection of 5.0 mg/kg proved lethal. Moreover, after three injections of 2.5 mg/kg rats displayed prominent signs of intoxication similar to those previously described by Dyer *et al.* [14] after a single administration of 6 mg/kg of trimethyltin. Acute effects of trimethyltin in dosages of 5–7 mg/kg have also been reported for locomotor activity [35] and radial-arm-maze performance [41]. The LD50 for trimethyltin has been reported to be between 7.4 mg/kg [14] and 12.6 mg/kg [8]. Therefore the ED50 for trimethyltin obtained after one flavor-toxicant pairing is between 25 and 42% of the LD50; these values are comparable to those for triethyltin.

Despite the fact that flavor aversions can be produced by trialkyltin compounds at dosages that are generally below those reported to appreciably affect other classes of behavior, very little is known about their mechanism(s) of action. Triethyltin's neurotoxic effects are in part related to the compound's inhibition of cellular respiration that results in cytotoxic hypoxia [2,34]. It would be interesting, therefore, to determine whether flavor aversions can be conditioned with other toxicants having similar effects, for example, hexachlorophene [9] and 2'-chloro-2,4-dinito-5',6-di(trifluoromethyl)-diphenylamine [23]. Although cyanide also inhibits cellular respiration [7] this compound was reported in two experiments to be ineffective in inducing flavor aversions [18,28]. These negative results may be due, however, to the particular experimental design and therefore not necessarily representative of the effects of compounds that inhibit cellular respiration.

Trimethyltin is thought to exert many of its effects via destruction of certain regions of the hippocampal formation and surrounding areas [1,8]. Although similar central effects have been produced by systemic administration of dipiperidinoethane [21,30] and kainic acid (e.g., [5]) whether or not these toxicants produce conditioned flavor aversions has yet to be determined. The impoartance of hippocampal involvement in the flavor aversions induced by trimethyltin could also be assessed by determining the effects of both prior lesioning of the hippocampus and neuropharmacological manipulations on the conditioning of flavor aversions. Alternatively, the flavor aversions induced by trimethyltin may be related to changes in gustatory sensitivity. This type of an effect would be consistent with alterations produced by trimethyltin in the visual, auditory and somatosensory systems [13, 16, 17]. In this regard further experiments are required that compare the flavor aversions and preferences produced by prototype flavored solutions (e.g., saccharin, quinine) in normal animals and in those pretreated with trimethyltin.

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